Docket No.: 1259-001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	)	
Bojidar M. Stankov	)	Group Art: 1616 Examiner: Choi, Frank I.
Serial No.: 09/854, 802	)	
Filed: May 14, 2001	)	

For: CONTROLLED RELEASE FORMULATIONS CONTAINING AN ACTIVE INGREDIENT, PREFERABLY MELATONIN AND THE METHOD OF PREPARATION

New York, NY 10036
May 31, 2005

MS Appeal
Commissioner for Patents
P.O. BOX 1450
Alexandria, VA 22313-1450

APPEAL BRIEF

This is an appeal from the final rejection of claims 16-18 and 20-24. This is the second Appeal Brief that has been filed in this application and under the provisions of 35 U.S.C.§134(a) no additional appeal fee is due.

(1) Real party in interest. The real party in interest is Ambros Pharma S.r.l.

(2) Related appeals and interferences. There are no related appeals or interferences.

(3) Status of the claims. Claims 16-18 and 20-24 are in the application and all of these claims have been finally rejected.

(4) Status of amendments. An Amendment is being filed herewith to delete the mark "--" at page 8. A petition, directed to the objection to claims 17, 18, 20, 21 22, and 24 is also being

filed as of even date herewith.

(5) Summary of invention. The present invention provides new formulations for the controlled release of melatonin that are able to "mimic" the physiological pattern of melatonin in the peripheral blood. The new formulations are designed to initially release melatonin quickly at first and thereafter slowly and gradually. The invention provides controlled release formulations, which are explicitly pointed out in the claims, as, medicines and nutritional or health food supplements for the treatment of sleep disturbances.

(6) Issues.

Are claims 16-18, 20-24 unpatentable under 35 U.S.C§112, first paragraph, as not being enabled other than for the formulation set forth in Example 1?

Are claims 16-18, 20-24 unpatentable over 35 U.S.C.§112, fiurst paragraph, as failing to comply with the written description requirement?

Are claims 16-18 and 20-24 unpatentable over 35 U.S.C.§112, second paragraph as being incomplete for omitting essential elements?

(7) Grouping of claims. Claim 16 is to be considered alone as it is not subject to any formal objection and claims 17, 18 and 20-24 are to be considered together and will stand or fall together.

(8) Argument.

The Rejection for Lack of Enablement

Claims 16-18 and 20-24 have been finally rejected under 35 U.S.C.§112, first paragraph, as not being based on an

enabling disclosure. The disclosure is directed to one of ordinary skill in the art which involves the making of controlled release formulations for oral administration. The text of the application at pages 7-8 provides a detailed recipe for making an embodiment of the invention and the specification at pages 5-7 also provides additional information that enables a skilled worker in the art to make and use the claimed invention. The rejection of record takes the view that the one working Example of the present application is insufficient to provide enablement and that undue experimentation would be required to make and use the invention commensurate in scope with the claims.

Claim 16 points out controlled release formulations of melatonin as noted at page 1, lines 26-29 of the specification. Claims 17 and 20 recite particular amounts of melatonin that are disclosed at page 4, lines 15-16. Claim 18 recites the preferred components as set forth in Example 1. Claim 19 specifies preferred in vitro release rates according to the method disclosed at page 9, lines 25-29 with the release values as disclosed at page 12, lines 1-5. Claim 21 points out a range of initial maximum plasma levels that are provided by the formulation of the invention as disclosed at page 6, lines 6-8. Claim 22 points out preferred in vivo release rates as disclosed at page 4, lines 1-7. Claims 23 and 24 point out the method of inducing and maintaining sleep in one suffering from a sleep disorder by the use of preferred formulations of the invention.

The provisions of 35 U.S.C.§112, first paragraph require that the disclosure of a patent application must be enabling. The enabling standard does not require that a claim point out each and every detail and component of a preferred embodiment. The requirement of the first paragraph of Section 112 is only properly chalenged when it is "reasonable" to conclude that one skilled in the art would be unable to carry out the claimed invention. In re Buchner, 18 USPQ2d 1331 (Fed. Cir. 1991). The present invention is concerned with controlled release of a single distinct entity, i.e. melatonin and not a

multiplicity of different active ingredients which could pose different formulation issues based on differences in solubility, density, particle size, pH, dosage size, metabolic rats, sites of absorption, stability etc. which typically cause problems in preparing controlled release formulations. The Examiner has not acknowledged that only a single active agent is pointed out by the finally rejected claims.

The text of Example 1 illustrates in great detail a working embodiment of a controlled release formulation of melatonin with the particular elements of the claims, i.e. HPMC, a lubricant, a volume excipient and a glidant. This information coupled with the general directions to those who are skilled in the art on pages 5 and 6 of the specification and the knowledge of the skilled artisan make it apparent that only with a minimum amount of experimentation, is it possible to make useful compositions within the scope of the claims other than the preferred embodiment of Example 1.

Enablement is determined on whether or not the extent of the experimentation necessary to practice the invention is reasonable. In re Wands, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) The Examiner has not evaluated the seven Wands factors whiuch are: (a) breadth of the claims; (b) nature of the invention; (c)state of the art; (d) level of skill in the art; (e) level of predictability; (f) amount of direction provided by the inventor; (g) existence of working examples; and (h) the quamntity of experimentation need to make and use the invention. When each of the Wands factors is evaulated, it is submitted that the present specification is enabling. For threses reasons, it is requested that the rejection for lack of enablement be reversed.

The text of claim 16 recites the principal ingredients as disclosed in the specification for making an operable composition. These claims are specific to a particular material and from this perspective are quite narrow. The recitation of the other ingredients is made in terms that are specific of to materials or classes of materials that are well known and are exemplified in the specification. The art of

making controlled relesase formulations for oral administration to humans has generated many thousands of patents in recent years and there are many textbooks and courses that have been devoted to this subject. Attached hereton ius a copy of an article titled: Review of Pharmaceutical Controlled Release Methods and Devices, Paul A. Steward, Lit. Rev. of Controlled Release Devices (1995). This review article notes at page 5 that the solubility of the drug is what determines the dosage properties. Since the present claims deal with only one substance, this variable is not present in the appealed claims. According to the standards set forth in MPEP§2164.04, the Examiner has not sustained the burden of showing a reasonable basis exists on which to challenge the claims.

The Rejection for Lack of a Written Description

Claims 16-18 and 20-24 have been finally rejected under 35 U.S.C.§112, first paragraph, as failing to comply with the written description requirement.

In evaluating a patent application for compliance with the written description requirement, there is a strong presumption that the claimed invention is present in the specification. In re Wertheim,191 USPQ 90, 96 (CCPA 1976). MPEP§ 2163 IIA. In addition, the Examiner has the initial burden of showing there is a lack of compliance with the written description requirement. MPEP§2163.04.

The reasons advanced by the Examiner are based on the use of the term "releases the melatonin within 5 hours..and within 10 minnutes" which the Examiner contends reads on release in less than the stated time period. The reported performance criteria has to do with release of a stated time within a certain elapsed time. It is not concerned with a release of less than the stated but only total release after a stated time. An example of this well known type of testing is illustrated in the attached U.S.P. 25 monograph on release testing which explains that it is the total amount released

during the stated time period which is the basis of the test and not the time required to achieve release. For these reasons, this ground of rejection should be reversed.

The Rejection Under 35 U.S.C.§ Second Paragraph

Claims 16-18 and 20-24 have been finally rejected under 35 U.S.C.§112, second paragraph, as being incomplete in that the elements of (a) granulation; (b) addition of retard excipients; and (c) applicaaation of melatonin soluition under pressure are essential for the preparation of the formulations. MPEP §2172.01 was cited as authority for this ground of rejection.

This ground of rejection is in error because the claims are directed to controlled release tablets and methods of inducing sleep and not to the process of making the claimed tablets which are used in the claimed methods. The disclosure of preferred methods of making the invention does not mean that the product claims that recite what the applicant regards as the invention, must recite the preferred methods or even critical processing steps in order to define the product of the invention. The product may be defined apart from the method by which it is made as a new composition of matter. For this reason, it is not necessary to import into the product claims the preferred process by which they are made. The applicant is not required to recite the processing details of the best mode for the practice in all claims merely because he has described the best mode in explicit language. MPEP§ 2172.01 does not require that essential processing procedures have to be recited in a product claim. Only essential elements have to be recited regarding the elements of the product. This has been done.

For these reasons, it is requested that the rejections

of record be reversed and patent protection allowed to an advance in the art.

Respectfully submitted,

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(9) Appendix.

16. A controlled release melatonin tablet which comprises:
(a) a slow release nucleus comprising melatonin, hydro xypropylmethylcellulose, a lubricant, a volume excipient and a glidant, wherein 95% of the melatonin is released within 5 hours in an oscillating tray containing gaastric/intestinal juice at 37°C;
(b) a fast release cortex coating on said nucleus which comprises melatonin, hydroxypropylmethylcellulose, a lubricant, a volume excipient and a glidant, wherein at least 95% of the melkatonin is released within 10 minutes in an oscillanting tray containing gastric/intestinal juice at 37°C.

17. The melatonin tablet as defined in claim 16 which comprises:
(a) a slow release nucleus comprising from 1 to 3 mg of melatonin, hydroxypropylmethylcellulose, a volume excipient and a glidant;
(b) a fast release cortex coating on said nucleus which comprises 0.5-1.5mg of melatonin, and hydroxypropylmethylcellulose, a volume excipient and a glidant.

18. The melatonin tablet as defined in claim 16 which consists essentially of:
(a) a slow release nucleus consisting essentially of melatonin, and hydroxypropylmethylcellulose, a volume excipient and a glidant;
(b) a fast release cortex coating on said nucleus which consist essentially of melatonin, and hydroxypropyl methylcellulose, a volume excipient and a glidant.

20. The melatonin tablet as defined in claim 16 which consists essentially of:
(a) a slow release nucleus consisting essentially of 1-3 mg of

melatonin, hydroxypropylmethylcellulose, a volume excipient and a glidant;
(b) a fast release cortex coating on said nucleus which consists essentially of 0.5-1.5 mg of melatonin with hydroxypropyl methylcellulose, a volume excipient and a glidant.

21. The melatonin tablet as defined in claim 16 which comprises:
(a) a slow release nucleus comprising melatonin, and hydroxypropylmethylcellulose, a volume excipient and a glidant;
(b) a fast release cortex coating on said nucleus comprising melatonin, hydroxypropyl methylcellulose, a volume excipient and a glidant wherein said tablet provides a maximum plasma level of 1,000 to 2,000 pg/ml of melatonin upon in vivo administration.

22. A controlled release melatonin tablet which comprises:
(a) a slow release nucleus comprising melatonin, hydroxypropylmethylcellulose, a volume excipient and a glidant which releases the melatonin over a 5 to 7 hour period in vivo;
(b) a fast release cortex coating on said nucleus comprising melatonin, hydroxypropylmethylcellulose, a volume excipient and a glidant which releases the melatonin in 5-10 minutes in vivo.

23. A method of inducing and maintaining sleep which comprises the administration of the formulation of claim 16 to one who suffers from a sleep disorder.

24. A method of inducing and maintaining sleep which comprises the administration of the formulation of claim 20 to one who suffers from a sleep disorder.

17. The nutritional food supplement tablet as defined in claim 16 which comprises:
(a) a slow release nucleus comprising from 1 to 3 mg of melatonin and hydroxypropylmethylcellulose;
(b) a fast release cortex coating on said nucleus which comprises 0.5-1.5mg of melatonin and hydroxypropylmethylcellulose.

18. The nutritional food supplement tablet as defined in claim 16 which consists essentially of:
(a) a slow release nucleus consisting essentially of melatonin and hydroxypropylmethylcellulose;
(b) a fast release cortex coating on said nucleus which consist essentially of melatonin and hydroxypropyl methylcellulose.

19. The nutritional food supplement tablet as defined in claim 16 which comprises:
(a) a slow release nucleus comprises melatonin and hydroxypropylmethylcellulose wherein 95% of the melatonin is released within 5 hours in an oscillating tray containing intestinal juice;
(b) a fast release cortex coating on said nucleus which comprises melatonin and hydroxypropyl methylcellulose wherein 95% of the melatonin is released within 10 minutes in an oscillating tray containing gastric juice.

20. The nutritional food supplement tablet as defined in claim 16 which consists essentially of:
(a) a slow release nucleus consisting essentially of 1-3 mg of melatonin with hydroxypropylmethylcellulose;
(b) a fast release cortex coating on said nucleus which consists essentially of 0.5-1.5 mg of melatonin with hydroxypropyl methylcellulose.

21. The nutritional food supplement tablet as defined in claim

16 which comprises:

(a) a slow release nucleus comprising melatonin and hydroxypropylmethylcellulose;

(b) a fast release cortex coating on said nucleus comprising melatonin and hydroxypropyl methylcellulose wherein said tablet provides a maximum plasma level of 1,000 to 2,000 pg/ml of melatonin upon in vivo administration.

22. A controlled release nutritional food supplement tablet which comprises:

(a) a slow release nucleus comprising melatonin and hydroxypropylmethylcellulose which releases the melatonin over a 5 to 7 hour period in vivo;

(b) a fast release cortex coating on said nucleus comprising melatonin which releases the melatonin in 5-10 minutes in vivo.

23. A method of inducing and maintaining sleep which comprises the administration of the formulation of claim 16 to one who suffers from a sleep disorder.

24. A method of inducing and maintaining sleep which comprises the administration of the formulation of claim 20 to one who suffers from a sleep disorder.

2002

USP 25 THE UNITED STATES PHARMACOPEIA

NF 20 THE NATIONAL FORMULARY

By authority of the United States Pharmacopeial Convention, Inc., meeting at Washington, D.C., April 12–16, 2000. Prepared by the Council of Experts and published by the Board of Trustees

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The designation on the cover of this publication, "USP NF 2002," is for ease of identification only. The publication contains two separate compendia: The Pharmacopeia of the United States Twenty-fifth Revision, and the National Formulary, Twentieth Edition.

UNITED STATES PHARMACOPEIAL CONVENTION, INC.
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⟨711⟩ DISSOLUTION

This test is provided to determine compliance with the dissolution requirements where stated in the individual monograph for a tablet or capsule dosage form. Of the types of apparatus described herein, use the one specified in the individual monograph. Where the label states that an article is enteric-coated, and a dissolution or disintegration test that does not specifically state that it is to be applied to enteric-coated articles is included in the individual monograph, the test for *Delayed-Release Articles* under *Drug Release* ⟨724⟩ is applied unless otherwise specified in the individual monograph. For hard or soft gelatin capsules and gelatin-coated tablets that do not conform to the *Dissolution* specification, repeat the test as follows. Where water or a medium with a pH of less than 6.8 is specified as the *Medium* in the individual monograph, the same *Medium* specified may be used with the addition of purified pepsin that results in an activity of 750,000 Units or less per 1000 mL. For media with a pH of 6.8 or greater, pancreatin can be added to produce not more than 1750 USP Units of protease activity per 1000 mL.

USP Reference Standards ⟨11⟩—*USP Prednisone Tablets RS (Dissolution Calibrator, Disintegrating). USP Salicylic Acid Tablets RS (Dissolution Calibrator, Nondisintegrating).*

Apparatus 1—The assembly consists of the following: a covered vessel made of glass or other inert, transparent material[1]; a motor; a metallic drive shaft; and a cylindrical basket. The vessel is partially immersed in a suitable water bath of any convenient size or placed in a heating jacket. The water bath or heating jacket permits holding the temperature inside the vessel at 37 ± 0.5° during the test and keeping the bath fluid in constant, smooth motion. No part of the assembly, including the environment in which the assembly is placed, contributes significant motion, agitation, or vibration beyond that due to the smoothly rotating stirring element. Apparatus that permits observation of the specimen and stirring element during the test is preferable. The vessel is cylindrical, with a hemispherical bottom and with one of the following dimensions and capacities: for a nominal capacity of 1 liter, the height is 160 mm to 210 mm and its inside diameter is 98 mm to 106 mm; for a nominal capacity of 2 liters, the height is 280 mm to 300 mm and its inside diameter is 98 mm to 106 mm; and for a nominal capacity of 4 liters, the height is 280 mm to 300 mm and its inside diameter is 145 mm to 155 mm. Its sides are flanged at the top. A fitted cover may be used to retard evaporation.[2] The shaft is positioned so that its axis is not more than 2 mm at any point from the vertical axis of the vessel and rotates smoothly and without significant wobble. A speed-regulating device is used that allows the shaft rotation speed to be selected and maintained at the rate specified in the individual monograph, within ±4%. Shaft and basket components of the stirring element are fabricated of stainless steel, type 316 or equivalent, to the specifications shown in Figure 1. Unless otherwise specified in the individual monograph, use 40-mesh cloth. A basket having a gold coating 0.0001 inch (2.5 µm) thick may be used. The dosage unit is placed in a dry basket at the beginning of each test. The distance between the inside bottom of the vessel and the basket is maintained at 25 ± 2 mm during the test.

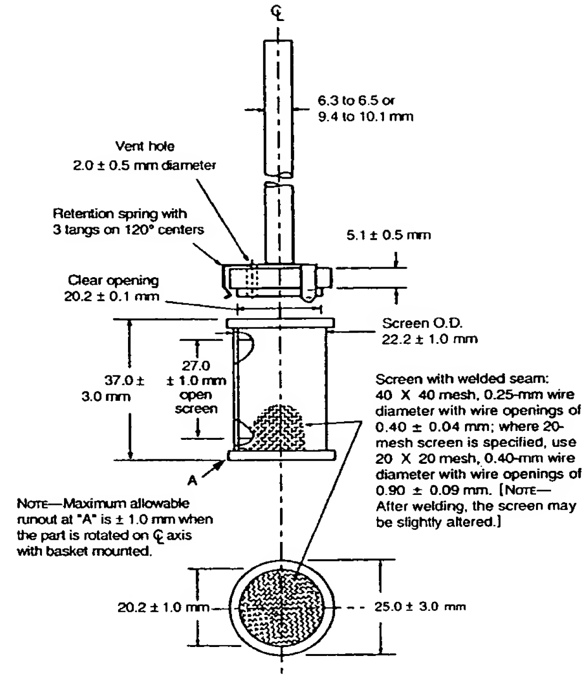

Fig. 1. Basket Stirring Element

Apparatus 2—Use the assembly from *Apparatus 1*, except that a paddle formed from a blade and a shaft is used as the stirring element. The shaft is positioned so that its axis is not more than 2 mm at any point from the vertical axis of the vessel and rotates smoothly without significant wobble. The vertical center line of the blade passes through the axis of the shaft so that the bottom of the blade is flush with the bottom of the shaft. The paddle conforms to the specifications shown in Figure 2. The distance of 25 ± 2 mm between the blade and the inside bottom of the vessel is maintained during the test. The metallic or suitably inert, rigid blade and shaft comprise a single entity. A suitable two-part detachable design may be used provided the assembly remains firmly engaged during the test. The paddle blade and shaft may be coated with a suitable inert coating. The dosage unit is allowed to sink to the bottom of the vessel before rotation of the blade is started. A small, loose piece of nonreactive material such as not more than a few turns of wire helix may be attached to dosage units that would otherwise float. Other validated sinker devices may be used.

[1] The materials should not sorb, react, or interfere with the specimen being tested.

[2] If a cover is used, it provides sufficient openings to allow ready insertion of the thermometer and withdrawal of specimens.

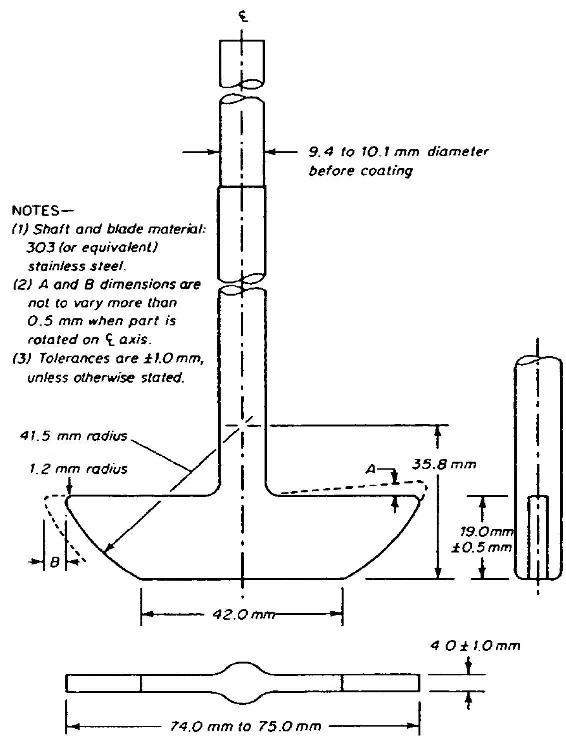

Fig. 2. Paddle Stirring Element

Apparatus Suitability Test—Individually test 1 tablet of the *USP Dissolution Calibrator, Disintegrating Type* and 1 tablet of *USP Dissolution Calibrator, Nondisintegrating Type*, according to the operating conditions specified. The apparatus is suitable if the results obtained are within the acceptable range stated in the certificate for that calibrator in the apparatus tested.

Dissolution Medium—Use the solvent specified in the individual monograph. If the *Dissolution Medium* is a buffered solution, adjust the solution so that its pH is within 0.05 unit of the pH specified in the individual monograph.

[NOTE—Dissolved gases can cause bubbles to form, which may change the results of the test. In such cases, dissolved gases should be removed prior to testing.[3]]

Time—Where a single time specification is given, the test may be concluded in a shorter period if the requirement for minimum amount dissolved is met. If two or more times are specified, specimens are to be withdrawn only at the stated times, within a tolerance of ±2%.

Procedure for Capsules, Uncoated Tablets, and Plain Coated Tablets—Place the stated volume of the *Dissolution Medium* (± 1%) in the vessel of the apparatus specified in the individual monograph, assemble the apparatus, equilibrate the *Dissolution Medium* to 37 ± 0.5°, and remove the thermometer. Place 1 tablet or 1 capsule in the apparatus, taking care to exclude air bubbles from the surface of the dosage-form unit, and immediately operate the apparatus at the rate specified in the individual monograph. Within the time interval specified, or at each of the times stated, withdraw a specimen from a zone midway between the surface of the *Dissolution Medium* and the top of the rotating basket or blade, not less than 1 cm from the vessel wall.

[NOTE—Replace the aliquots withdrawn for analysis wi volumes of fresh *Dissolution Medium* at 37° or, where i shown that replacement of the medium is not necessary, co the volume change in the calculation. Keep the vessel cov the duration of the test, and verify the temperature of the mi der test at suitable times.] Perform the analysis as directed i dividual monograph.[4] Repeat the test with additional dosa units.

If automated equipment is used for sampling and the app modified, validation of the modified apparatus is needed to sl there is no change in the agitation characteristics of the test.

Where capsule shells interfere with the analysis, remove tents of not less than 6 capsules as completely as possible. solve the empty capsule shells in the specified volume of *Dis Medium*. Perform the analysis as directed in the individua graph. Make any necessary correction. Correction factors gre 25% of the labeled content are unacceptable.

Procedure for a Pooled Sample for Capsules, Uncoa blets, and Plain Coated Tablets—Use this procedure wher *dure for a Pooled Sample* is specified in the individual mo Proceed as directed under *Procedure for Capsules, Uncoated and Plain Coated Tablets*. Combine equal volumes of the fil lutions of the six or twelve individual specimens withdrawn, the pooled sample as the test solution. Determine the average of the active ingredient dissolved in the pooled sample.

Interpretation—

Unit Sample—Unless otherwise specified in the individu graph, the requirements are met if the quantities of active in dissolved from the units tested conform to the accompanyin tance Table. Continue testing through the three stages unles sults conform at either S_1 or S_2. The quantity, Q, is the an dissolved active ingredient specified in the individual monog pressed as a percentage of the labeled content; the 5%, 15%, values in the *Acceptance Table* are percentages of the labelec so that these values and Q are in the same terms.

Acceptance Table

Stage	Number Tested	Acceptance Criteria
S_1	6	Each unit is not less than Q +
S_2	6	Average of 12 units (S_1 + S_2) is or greater than Q, and no un than Q - 15%.
S_3	12	Average of 24 units (S_1 + S_2 equal to or greater than Q, n than 2 units are less than Q and no unit is less than Q - 2

Pooled Sample—Unless otherwise specified in the in monograph, the requirements are met if the quantities of acti dient dissolved from the pooled sample conform to the accom *Acceptance Table for a Pooled Sample*. Continue testing thr three stages unless the results conform at either S_1 or S_2. The Q, is the amount of dissolved active ingredient specified in vidual monograph, expressed as a percentage of the labeled

Acceptance Table for a Pooled Sample

Stage	Number Tested	Acceptance Criteria
S_1	6	Average amount dissolved is than Q + 10%.
S_2	6	Average amount dissolved (S_1 equal to or greater than Q + 5
S_3	12	Average amount dissolved (S S_3) is equal to or greater than

[3] One method of deaeration is as follows: Heat the medium, while stirring gently, to about 41°, immediately filter under vacuum using a filter having a porosity of 0.45 µm or less, with vigorous stirring, and continue stirring under vacuum for about 5 minutes. Other validated deaeration techniques for removal of dissolved gases may be used.

[4] If test specimens are filtered, use an inert filter that does not cause a of the active ingredient or contain extractable substances that would with the analysis.

⟨721⟩ DISTILLING RANGE

To determine the range of temperatures within which an official liquid distils, or the percentage of the material that distils between two specified temperatures, use Method I or Method II as directed in the individual monograph. The *lower limit* of the range is the temperature indicated by the thermometer when the first drop of condensate leaves the tip of the condenser, and the *upper limit* is the Dry Point, i.e., the temperature at which the last drop of liquid evaporates from the lowest point in the distillation flask, without regard to any liquid remaining on the side of the flask, or the temperature observed when the proportion specified in the individual monograph has been collected.

[NOTE—Cool all liquids that distil below 80° to between 10° and 15° before measuring the sample to be distilled.]

Method I

Apparatus—Use apparatus similar to that specified for *Method II*, except that the distilling flask is of 50- to 60-mL capacity, and the neck of the flask is 10 to 12 cm long and 14 to 16 mm in internal diameter. The perforation in the upper insulating board, if one is used, should be such that when the flask is set into it, the portion of the flask below the upper surface of the insulating material has a capacity of 3 to 4 mL.

Procedure—Proceed as directed for *Method II*, but place in the flask only 25 mL of the liquid to be tested.

METHOD II

Apparatus—Use an apparatus consisting of the following parts:

Distilling Flask—A round-bottom distilling flask, of heat-resistant glass, of 200-mL capacity, and having a total length of 17 to 19 cm and an inside neck diameter of 20 to 22 mm. Attached about midway on the neck, approximately 12 cm from the bottom of the flask, is a side-arm 10 to 12 cm long and 5 mm in internal diameter, which forms an angle of 70° to 75° with the lower portion of the neck.

Condenser—A straight glass condenser 55 to 60 cm in length with a water jacket about 40 cm in length, or a condenser of other design having equivalent condensing capacity. The lower end of the condenser may be bent to provide a delivery tube, or it may be connected to a bent adapter that serves as a delivery tube.

Insulating Boards—Two pieces of insulating board, 5 to 7 mm thick and 14 to 16 cm square, suitable for confining the heat to the lower part of the flask. Each board has a hole in its center, and the two boards differ only with respect to the diameter of the hole, i.e., the diameters are 4 and 10 cm, respectively. In use, the boards are placed one upon the other, and resting on a tripod or other suitable support, with the board having the larger hole on top.

Receiver—A 100-mL cylinder graduated in 1-mL subdivisions.

Thermometer—In order to avoid the necessity for an emergent stem correction, an accurately standardized, partial-immersion thermometer having the smallest practical subdivisions (not greater than 0.2°) is recommended. Suitable thermometers are available as the ASTM E-1 series 37C through 41C, and 102C through 107C (see *Thermometers* ⟨21⟩). When placed in position, the stem is located in the center of the neck and the top of the contraction chamber (or bulb, if 37C or 38C is used) is level with the bottom of the outlet to the side-arm.

Heat Source—A small Bunsen burner or an electric heater or mantle capable of adjustment comparable to that possible with a Bunsen burner.

Procedure—Assemble the apparatus, and place in the flask 100 mL of the liquid to be tested, taking care not to allow any of the liquid to enter the side-arm. Insert the thermometer, shield the entire burner and flask assembly from external air currents, and apply heat, regulating it so that between 5 and 10 minutes elapse before the first drop of distillate falls from the condenser. Continue the distillation at a rate of 4 to 5 mL of distillate per minute, collecting the distillate in the receiver. Note the temperature when the first drop of distillate falls from the condenser, and again when the last drop of liquid evaporates from the bottom of the flask or when the specified percentage has distilled over. Correct the observed temperature readings for any variation in the observed ambient barometric pressure from the normal (760 mm), adding if the pressure is lower or subtracting if the pressure is higher than 760 mm, and apply the emergent stem correction where necessary. Unless otherwise specified in the individual monograph, allow 0.1° for each 2.7 mm (0.037° per mm) of variation.

⟨724⟩ DRUG RELEASE

This test is provided to determine compliance with drug-release requirements where specified in individual monographs. Use the apparatus specified in the individual monograph. Replace the aliquots withdrawn for analysis with equal volumes of fresh *Dissolution Medium* at 37° or, where it can be shown that replacement of the medium is not necessary, correct for the volume change in the calculation.

[NOTE—Medium replacement is not necessary for *Apparatus 4*, which is a continuous-flow system.] Keep the vessel covered for the duration of the test, and verify the temperature of the mixture under test at suitable times.

EXTENDED-RELEASE ARTICLES—GENERAL DRUG RELEASE STANDARD

Apparatus 1 and Apparatus 2

Apparatus—Proceed as directed under *Dissolution* ⟨711⟩.

Apparatus Suitability Test, Dissolution Medium, and Procedure—Proceed as directed under *Dissolution* ⟨711⟩.

Time—The test-time points, generally three, are expressed in hours. Specimens are to be withdrawn within a tolerance of ±2% of the stated time.

Interpretation—Unless otherwise specified in the individual monograph, the requirements are met if the quantities of active ingredient dissolved from the units tested conform to *Acceptance Table 1*. Continue testing through the three levels unless the results conform at either L_1 or L_2. Limits on the amounts of active ingredient dissolved are expressed in terms of the percentage of labeled content. The limits embrace each value of Q_i, the amount dissolved at each specified fractional dosing interval. Where more than one range is specified in the individual monograph, the acceptance criteria apply individually to each range.

Acceptance Table 1

Level	Number Tested	Criteria
L_1	6	No individual value lies outside each of the stated ranges and no individual value is less than the stated amount at the final test time.
L_2	6	The average value of the 12 units (L_1 + L_2) lies within each of the stated ranges and is not less than the stated amount at the final test time; none is more than 10% of labeled content outside each of the stated ranges; and none is more than 10% of labeled content below the stated amount at the final test time.

Review of Pharmaceutical Controlled Release Methods and Devices.

By Paul A. Steward.

Contents:

Go to Top of Page.

Review of Pharmaceutical Controlled Release Methods and Devices.

1. Introduction.

An example of the utilisation of latex coatings is by the pharmaceutical industry, in the preparation of drug coatings, and industries where similar technology may be employed in dispersion systems that might previously have relied on the periodic addition of a chemical. The aim of this Page is to introduce some of the ideas from the literature for the designs of various (controlled) release methods.

Go to Top of Page.

2. Polymers and the Pharmaceutical Industry.

Polymers have gained in importance in the pharmaceutical industry as both drug encapsulants and vehicles of drug carriage: either protecting an active agent during its passage through the body (or in storage by preventing moisture ingress [Udeala & Aly (1989)]) until its release, or controlling its release. A conventional (*eg*, sugar) tablet coating has the disadvantageous side effect of delivering what may be an initially too high and, hence, harmful, dose of active agent (typically, drug is rapidly released from its dosage form, reaching a maximum concentration, which then decays exponentially until the next administration), to regions of the body where the drug may not be at its most effective; when the general aim of any medication is to generate a response in a specific area or organ of the body requiring treatment. These problems can be overcome to some extent by sustained/retarded release, and/or selective delivery of the drug to the targeted organs [*eg*, Gardner (1983), Gregoriadis (3 references: 1977, 1986, 1988), Poznansky & Juliano (1984), Tomlinson & Davis (1986)]. **Advantages of controlled release** devices thus possibly include: delivery to the required site; delivery at the required rate; fewer applications; reduced dangers of overdose, or side effects; and also economic advantages by virtue of more efficient dosage, at the expense of possibly more complicated fabrication. Much of the relevant literature is very precise in that it either concentrates, for example, on a specific type of polymer offering suitable transport characteristics for an individual permeant, or concentrates on a range of permeants transported through a single polymer type, or concentrates on a unique application.

Go to Top of Page.

3. Drug Delivery.

In recent years, there have been numerous developments in polymeric carriers and controlled release systems (some commercially available devices have been described by Lonsdale (1982)). A few examples mentioned in the literature include:

- films with the drug *in* a **polymer matrix** [*eg*, Davis & Illum (1988), Douglas *et al.* (1987), Oppenheim (1981)] **(monolithic devices)**;
- the drug contained *by* the polymer **(reservoir devices)** [*eg*, Lehmann *et al.* (1979)];
- polymeric colloidal particles or microencapsulates (**microparticles, microspheres** or **nanoparticles**) in the form of reservoir and matrix devices [*eg*, Douglas *et al.* (1987), Oppenheim (1981)];
- drug contained by a polymer containing a **hydrophilic** and/or **leachable additive** *eg*, a second polymer, surfactant or plasticiser, etc. to give a porous device, or a device in which the drug release may be osmotically 'controlled' (both reservoir and matrix devices) [*eg*, Fites *et al.* (1970), Muhammad *et al.* (1991), Samuelov *et al.* (1979), Zentner *et al.* (1985)];
- **enteric coatings** (ionise and dissolve at a suitable pH) [*eg*, Muhammad *et al.* (1991)];
- (soluble) polymers with (covalently) attached **'pendant' drug** molecules [Chafi *et al.* (3 references: 1988, 1991 & 1992), Duncan & Kopacek (1984), Scholsky & Fitch (1986)];
- devices where release rate is controlled dynamically: *eg*, the **osmotic pump** [Theeuwes (1975)].

More recently, speculation in the literature has centred around the possibility of using the recently discovered large cage-like molecules such as the C_{60} Buckminster-fullerenes [Culotta & Koshland (1991)] (**'Buckyballs'**) (1985 [Taubes (1991)]), or hyperbranched (starburst) dendrimers [Alper (1991)] (late 1970s). The latter are large, 350,000 molecular weight, uniform, hollow, polymer spheres with a surface area comparable to that of carbon black (1,000 m^2 g^{-1}). Some of these hyperbranched dendrimers are even water soluble.

Ideally, the delivery mechanism should control the rate of release. The ideal release mechanism should be at a constant rate (zero order). However, changing concentration gradients or additive leaching leading to porosity, etc., within the release devices typically mean that the release of the drug varies as a function of time.

Lehmann *et al* (1979). give four advantages of the coating of small drug particles, as opposed to single tablets:

- coated particles will distribute over the stomach and intestine to give a more uniform release and reduce the effects due to local conditions such as pH;
- a drug can be coated with different coatings, or thickness of coating, to give the required release profile;
- disparate active ingredients can be coated individually; and
- the danger of dosage overdose due to coat faults or, alternatively, incomplete release of drug is reduced.

The size of the dosage form may be controlled by factors such as the potency of the drug, and the amount required (although this may be controlled to some extent by the use of either fillers, to enlarge the formulation, or division of the dose into more than one 'packet' to decrease physical size). Duration of release of the drug is a further factor that must be considered (including the transit time of the dosage form through the body, or to the required site of release) as must the means of administration (*eg*, oral or other means, *ie*, parenteral).

Polymers used in sustained release coatings are necessarily biocompatible, and ideally biodegradable. The literature gives examples of both naturally occurring polymers such as Aquacoat® (FMC Corporation, Food & Pharmaceutical Products Division, Philadelphia, USA) (ethylcellulose mechanically spheronised to sub-micron sized, aqueous based, pseudo-latex dispersions), and also synthetic polymers such as the Eudragit® (Röhm Pharma, Weiterstadt.) range of poly(acrylate, methacrylate) copolymers. (Comparisons of aqueous versus solvent cast coatings have been made by Hogan (1982).)

Go to Top of Page.

3.1 Reservoir Devices.

A typical approach to controlled release is to encapsulate or contain the drug entirely (*eg*, as a core [*eg*, see previous Lehmann reference]), within a polymer film or coat (*ie*, microcapsules or spray/pan coated cores). Film coating (with particular reference to polymers and their additives) has been reviewed by Kala *et al.* (1979), whilst microencapsulation has been reviewed by Arshady (3 references: 1989, 1990, & 1990).

The various factors that can affect the diffusion process may readily be applied to reservoir devices (*eg*, the effects of additives, polymer functionality {and, hence, sink-solution pH} porosity, film casting conditions, etc.) and, hence, the choice of polymer must be an important consideration in the development of reservoir devices. Modelling the release characteristics of reservoir devices (and monolithic devices) in which the transport of the drug is by a solution-diffusion mechanism therefore typically involves a solution to Fick's second law (unsteady-state conditions; concentration dependent flux) for the relevant boundary conditions. When the device contains dissolved active agent, the rate of release decreases exponentially with time as the concentration (activity) of the agent (*ie*, the driving force for release) within the device decreases (*ie*, first order release). If, however, the active agent is in a saturated suspension, then the driving force for release is kept constant (zero order) until the device is no longer saturated [deV Naylor (book) and Stannett *et al.* (1979)]. Alternatively the release-rate kinetics may be desorption controlled, and a function of the square root of time.

Transport properties of coated tablets, may be enhanced compared to free-polymer films, due to the enclosed nature of the tablet core (permeant) which may enable the internal build-up of an osmotic pressure which will then act to force the permeant out of the tablet [*eg*, Zentner *et al.* (1985)].

Li & Peck (1989) investigated the effect of deionised water on salt containing tablets coated in poly(ethylene glycol) (PEG)-containing silicone elastomer, and also the effects of water on free films. The release of salt from the tablets was found to be a mixture of diffusion through water filled pores, formed by hydration of the coating, and osmotic pumping. KCl transport through films containing just 10% PEG was negligible, despite extensive swelling observed in similar free films, indicating that porosity was necessary for the release of the KCl which then occurred by 'trans-pore diffusion.' Coated salt tablets, shaped as disks, were found to swell in deionised water and change shape to an oblate spheroid as a result of the build-up of internal hydrostatic pressure: the change in shape providing a means to measure the 'force' generated. As might be expected, the osmotic force decreased with increasing levels of PEG content. The lower PEG levels allowed water to be imbibed through the hydrated polymer; whilst the porosity resulting from the coating dissolving at higher levels of PEG content (20 to 40%) allowed the pressure to be relieved by the flow of KCl.

Li developed methods and equations, which by monitoring (independently) the release of two different salts (*eg*, KCl and NaCl) allowed the calculation of the relative magnitudes that both osmotic pumping and trans-pore diffusion contributed to the release of salt from the tablet. At low PEG levels, osmotic flow was increased to a greater extent than was trans-pore diffusion due to the generation of only a low pore number density: at a loading of 20%, both mechanisms contributed approximately equally to the release. The build-up of hydrostatic pressure, however, decreased the osmotic inflow, and osmotic pumping. At higher loadings of PEG, the hydrated film was more porous and less resistant to outflow of salt. Hence, although the osmotic pumping increased (compared to the lower loading), trans-pore diffusion was the dominant release mechanism. An osmotic release mechanism has also been reported for microcapsules containing a water soluble core [Benita & Donbrow (1982)].

Go to Top of Page.

3.2 Monolithic Devices (Matrix Devices).

Monolithic (matrix) **devices** are possibly the most common of the devices for controlling the release of drugs. This is possibly because they are relatively easy to fabricate, compared to reservoir devices, and there is not the danger of an accidental high dosage that could result from the rupture of the membrane of a reservoir device. In such a device the active agent is present as a dispersion within the polymer matrix, and they are typically formed by the compression of a polymer/drug mixture or by dissolution or melting. The dosage release properties of monolithic devices may be dependent upon the solubility of the drug in the polymer matrix or, in the case of porous matrixes, the solubility in the sink solution within the particle's pore network, and also the tortuosity of the network [Singh *et al.* (1968)] (to a greater extent than the permeability of the film), dependent on whether the drug is dispersed in the polymer or dissolved in the polymer. For low loadings of drug, (0 to 5% W/V) the drug will be released by a solution-diffusion mechanism (in the absence of pores). At higher loadings (5 to 10% W/V), the release mechanism will be complicated by the presence of cavities formed near the surface of the device as the drug is lost: such cavities fill with fluid from the environment increasing the rate of release of the drug.

It is common to add a plasticiser (*eg*, a poly(ethylene glycol)), or surfactant, or adjuvant (*ie*, an ingredient which increases effectiveness), to matrix devices (and reservoir devices) as a means to enhance the permeability (although, in contrast, plasticiser may be fugitive, and simply serve to aid film formation [Nakagami *et al.* (1991)] and, hence, decrease permeability - a property normally more desirable in polymer paint coatings). It was noted by Donbrow & Friedman (1975), that the leaching of PEG acted to increase the permeability of (ethyl cellulose) films linearly as a function of PEG loading by increasing the porosity, however, the films retained their barrier properties, not permitting the transport of electrolyte. It was deduced that the enhancement of their permeability was as a result of the effective decrease in thickness caused by the PEG leaching. This was evinced from plots of the cumulative permeant flux per unit area as a function of time and film reciprocal thickness at a PEG loading of 50% W/W: plots showing a linear relationship between the rate of permeation and reciprocal film thickness, as expected for a (Fickian) solution-diffusion type transport mechanism in a homogeneous membrane. Extrapolation of the linear regions of the graphs to the time axis gave positive intercepts on the time axis: the magnitude of which decreased towards zero with decreasing film thickness. These changing lag times were attributed to the occurrence of two diffusional flows during the early stages of the experiment (the flow of the 'drug' and also the flow of the PEG), and also to the more usual lag time during which the concentration of permeant in the film is building-up. Caffeine, when used as a permeant, showed negative lag times. No explanation of this was forthcoming, but Donbrow noted that caffeine exhibited a low partition coefficient in the system, and that this was also a feature of aniline permeation [Serota *et al.* (1970)] through polyethylene films which showed a similar negative time lag.

Efentakis *et al.* (2 references: Buckton 1991, & 1991). investigated the effects of added surfactants on (hydrophobic) matrix devices. It was thought that surfactant may increase the drug release rate by three possible mechanisms: (i) increased solubilisation, (ii) improved 'wettability' to the dissolution media, and (iii) pore formation as a result of surfactant leaching. For the system studied (Eudragit® RL 100 and RS 100 plasticised by sorbitol, Flurbiprofen as the drug, and a range of surfactants) it was concluded that improved wetting of the tablet led to only a partial improvement in drug release (implying that the release was diffusion, rather than dissolution, controlled), although the effect was greater for Eudragit® RS than Eudragit® RL, whilst the greatest influence on release was by those surfactants that were more soluble due to the formation of 'disruptions' in the matrix allowing the

dissolution medium access to within the matrix. This is of obvious relevance to a study of latex films which might be suitable for pharmaceutical coatings, due to the ease with which a polymer latex may be prepared with surfactant as opposed to surfactant-free. Differences were found between the two polymers - with only the Eudragit® RS showing interactions between the anionic/cationic surfactant and drug. This was ascribed to the differing levels of quaternary ammonium ions on the polymer.

Composite devices consisting of a polymer/drug matrix coated in a polymer containing no drug also exist. Such a device was constructed by Bodmeier & Paeratakul (1990) from aqueous Eudragit® latices, and was found to give zero order release by diffusion of the drug from the core through the shell. Laghoueg *et al.* (1989). similarly produced a polymer core containing the drug, but coated this with a shell that was eroded by the gastric fluid. The rate of release of the drug was found to be relatively linear (a function of the rate limiting diffusion process through the shell) and inversely proportional to the shell thickness, whereas the release from the core alone was found to decrease with time.

Go to Top of Page.

3.3 Other methods of drug carriage and controlled release.

3.3.1 Variations on the theme of microspheres.

Kawashima *et al.* (2 references: both 1992). have described methods for the preparation of hollow microspheres ('microballoons') with the drug dispersed in the sphere's shell, and also highly porous matrix-type microspheres ('microsponges'). The microsponges were prepared by dissolving the drug and polymer in ethanol. On addition to water, the ethanol diffused from the emulsion droplets to leave a highly porous particle. Variation of the ratios of drug and polymer in the ethanol solution gave control over the porosity of the particle, and the drug release properties were fitted to the Higuchi model (2 references: 1961 & 1963).

The hollow microspheres were formed by preparing a solution of ethanol/dichloro-methane containing the drug and polymer. On pouring into water, this formed an emulsion containing the dispersed polymer/drug/solvent particles, by a coacervation-type process, from which the ethanol (a good solvent for the polymer) rapidly diffused precipitating polymer at the surface of the droplet to give a hard-shelled particle enclosing the drug, dissolved in the dichloromethane. At this point, a gas phase of dichloromethane was generated within the particle which, after diffusing through the shell, was observed to bubble to the surface of the aqueous phase. The hollow sphere, at reduced pressure, then filled with water, which could be removed by a period of drying. (No drug was found in the water.) A suggested use of the microspheres was as floating drug delivery devices for use in the stomach.

Go to Top of Page.

3.3.2 Pendent devices.

Scholsky and Fitch (1986) developed a means of attaching a range of drugs such as analgesics and antidepressants, etc., by means of an ester linkage to poly(acrylate) ester latex particles prepared by aqueous emulsion polymerisation. These latices when passed

through an ion exchange resin such that the polymer end groups were converted to their strong acid form could 'self-catalyse' the release of the drug by hydrolysis of the ester link.

Chafi *et al.* (2 references: 1988 & 1992). cite a number of papers where drugs have been attached to polymers, and also where monomers have been synthesised with a pendent drug attached. The research group have also prepared their own dosage forms in which the drug is bound to a biocompatible polymer by a labile chemical bond [Chafi *et al.* (2 references: 1988 & 1992)]: *eg*, polyanhydrides prepared from a substituted anhydride (itself prepared by reacting an acid chloride with the drug: methacryloyl chloride and the sodium salt of methoxy benzoic acid) were used to form a matrix with a second polymer (Eudragit® RL) which released the drug on hydrolysis in gastric fluid. Chafi *et al.* (1991) has also described the use of polymeric Schiff bases suitable for use as carriers of pharmaceutical amines.

Go to Top of Page.

3.3.3 Enteric films.

Enteric coatings consist of pH sensitive polymers. Typically the polymers are carboxylated and interact (swell) very little with water at low pH, whilst at high pH the polymers ionise causing swelling, or dissolving of the polymer. Coatings can therefore be designed to remain intact in the acidic environment of the stomach (protecting either the drug from this environment or the stomach from the drug), but to dissolve in the more alkaline environment of the intestine.

Go to Top of Page.

3.3.4 Osmotically controlled devices.

The osmotic pump is similar to a reservoir device but contains an osmotic agent (*eg*, the active agent in salt form) which acts to imbibe water from the surrounding medium via a semi-permeable membrane. Such a device, called the **'elementary osmotic pump'**, has been described by Theeuwes (1975). Pressure is generated within the device which forces the active agent out of the device via an orifice (of a size designed to minimise solute diffusion, whilst preventing the build-up of a hydrostatic pressure head which has the effect of decreasing the osmotic pressure and changing the dimensions {volume} of the device). Whilst the internal volume of the device remains constant, and there is an excess of solid (saturated solution) in the device, then the release rate remains constant delivering a volume equal to the volume of solvent uptake.

Go to Top of Page.

3.3.5 Electrically stimulated release devices.

Yuk *et al.* (1992). prepared monolithic devices using polyelectrolyte gels which swelled when, for example, an external electrical stimulus was applied, causing a change in pH. The release could be modulated, by the current, giving a pulsatile release profile.

Go to Top of Page.

3.3.6 Hydrogels.

Hydrogels find a use in a number of biomedical applications, in addition to their use in drug matrices (*eg*, soft contact lenses, and various 'soft' implants, etc.) [Pedley *et al.* (1980), and Ratner & Hoffman (1976)].

Adapted from: Modification of the Permeability of Polymer Latex Films., Nottingham Trent University PhD Thesis, 1995.

Go to Top of Page.

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Go to Top of Page.
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